Asian Journal of Basic Science & Research
Volume 6, Issue 4, Pages 115-123, October-December 2024

Mixed Ligand Copper Complexes of Cimetidine: Synthesis, Spectroscopic and Physico-chemical Characterization

Olufunso O. Abosede[1*] & Stephen P. Osi[2]

[1,2]*Department of Chemistry, Federal University Otuoke, Otuoke, via Yenagoa, Bayelsa State, Nigeria.*
Corresponding Author (Olufunso O. Abosede) Email: abosedeoo@fuotuoke.edu.ng[*]

DOI: http://doi.org/10.38177/AJBSR.2024.6409

Article Received: 11 October 2024 *Article Accepted: 19 December 2024* *Article Published: 27 December 2024*

ABSTRACT

The greener and cost-effective synthesis of copper complex of Cimetidine (Cime) as primary ligand with one of imidazole (imi), 2,2'-bipyridine (bpy) and 1,10-phenathroline (phen) as secondary ligands respectively are described. The synthesis involves the use of distilled water as solvent and refluxing. This method serves great advantages as it is environmentally friendly, with simple work-up procedures and short reaction time with excellent yield. The complexes were synthesized by direct dissolving of the metal salt ($CuSO_4$) in water, followed by the addition of the cimetidine and secondary ligands where applicable, stirring and filtration. The residue was dried and collected, and the filtrate kept for slow evaporation resulting in fine crystals. The obtained products were characterized by their UV-Vis and FTIR spectra, their solubility determined in various solvents and the melting point determined with the Stuarts Melting point (SMP11) apparatus. Metal complexes with formula of Cu(II)-L_1L_2 were deduced where L_1=Cimetidine (Cime), and L_2=Imidazole (imi), Bipyridine bpy) or phenathroline (Phen).

Keywords: Cimetidine; Imidazole; 2,2'-bipyridine; 1,10-phenathroline; Polypyridyl; Spectrophotometry; Physico-chemical; Characterization.

1. Introduction

Coordination compounds, also known as complexes, are created through the interaction of Lewis acids (electron pair acceptors) and Lewis bases (electron pair donors). Lewis acids, which must have empty orbitals to accept these electron pairs. Transition metals like Fe, Co, and Cu, as well as compounds like BF_3 and $BeCl_2$ with empty p-orbitals, and ions like H^+ from main block elements, can all act as Lewis acids. Lewis bases contain hetero atoms with lone pairs. Examples of Lewis base include H_2O, NH_3, CO, as well as anions such as halides (F-, Cl-, Br-) and cyanide (CN-). The characteristics of the ligand, such as its alkalinity, bonding, and chelate effects, play a significant role in determining the formation of complex compounds (Direm *et al.*, 2018).

The study of coordination compounds has its roots in the work of Alfred Werner (1866-1919), a Swiss chemist who was the first in his country to win the Nobel Prize in Chemistry for his advancements in coordination chemistry. Werner conducted experiments involving the synthesis, characterization, and analysis of the physical and chemical properties of compounds using basic precipitation techniques. Alfred Werner's contributions to coordination chemistry laid the groundwork for subsequent chemists to elucidate the characteristics, structures, properties, and uses of these compounds (Fricker, 2007). One of such metal complexes includes Cisplatin (cis-$Pt(NH_3)_2Cl_2$), known for its application in treating cancer, particularly testicular cancer, was discovered by Barnett Rosenberg in the 1960s. During his research on the similarity between the mitotic spindle of dividing cells and the alignment of iron filings around a magnetic field, Rosenberg made this groundbreaking discovery. This revelation of the antitumor properties of cisplatin and its derivatives played a crucial role in the development of medicinal inorganic chemistry (Trudu *et al.*, 2015) which has led to the syntheses of varieties of metal complexes for various applications (Frota *et al.*, 2024; Obaleye and Abosede, 2019; Ogodo, and Abosede 2019). Various metal complexes have shown great efficacy against a range of disease-causing organisms (Abosede *et al.*, 2016). However, their

clinical utility is restricted due to concerns regarding toxicity levels and the development of drug resistance (Storr, *et al.*, 2006).

1.1. Study Objectives

The objectives of this study are: (1) To synthesize and characterize ternary copper complexes of cimetidine (cime) with imidazole (imi), 2,2-bipyridine (bpy), and 1,10-phenanthroline (phen), (2) To deduce the structures of the synthesized complexes using UV-Vis and FTIR spectroscopies, (3) To investigate the physico-chemical properties of the synthesized complexes, including solubility in different solvents, and (4) To determine the melting points of the complexes and their ligands using the Stuart melting point (SMP 11) apparatus.

2. Materials and Methods

2.1. Materials

The metal salt of metals such as copper sulfate ($CuSO_4$), with cimetidine, and ligands such as imidazole (Imi), 2,2-bypiridine (Bpy), 1,10-phenanthroline (Phen) and mebendazole (Meb) were all gotten from commercial sources (pharmaceutical industry) and were used without any further purification. The complexes (materials) were further characterized using the JASCO V-730 Ultraviolet-Visible spectrophotometer, the melting points of the complexes were determined using Stuart melting point (SMP 11) apparatus, and the solubility was determined in these solvents: methanol, ethanol, distilled water, acetone and DMF.

2.2. Synthesis of Complexes

2.2.1. Synthesis of [CuCime]SO_4, Complex 1

0.195 g (1 mM) of copper sulfate was dissolved in 10 ml of sodium hydroxide NaOH solution of 0.2 M in a round bottom flask of 50 ml, swirled to dissolve completely with a light blue coloured solution. 0.252 g (1 mM) of cimetidine was added into the solution, it dissolved completely and the colour changed from light blue to green. The solution was stirred on a Tekno vetro magnetic stirrer for about one (1) hour until no more colour change. It was then filtered into a beaker. The filtrate was kept in a cupboard for 5 days to which it had formed dark green crystals. The solution was decanted and the crystals were picked into a glass vial and kept for analysis. Percentage yield (crystals) was 0.63 g, (14%). UV-Vis (DMF): 313 nm, 370 nm, 755 nm. UV-Vis (ethanol): 227 nm, 278 nm.

2.2.2. Synthesis of [CuCime-imi]SO_4, Complex 2

0.195 g (1 mM) of copper sulfate was dissolved in 10 ml of sodium hydroxide (NaOH) solution of 0.2 M in a round bottom flask of 50 ml, swirled to dissolve completely with a blue-coloured solution. 0.252 g (1 mM) of cimetidine was added into the solution, the colour changed from blue to green instantly. The solution was stirred on a Tekno vetro magnetic stirrer for one (1) hour. 0.152 g (2 mM) of imidazole dissolved in 1ml of distilled water was added into the solution, the colour changed from green to blue immediately and stirring continued for another one (1) hour and the colour uniformed. The solution was filtered into a beaker, the filtrate was kept in a cupboard for 5 days to which it had formed dark blue crystals. The solution was decanted and the crystals were picked into a glass vial and kept for analysis. Percentage yield was 0.52 g, (84%). UV-Vis (DMF): 315 nm, 370 nm, 693 nm.

2.2.3. Synthesis of [CuCime-bpy]SO_4, complex 3

0.391 g (2 mM) of copper sulfate was dissolved in 4 ml of sodium hydroxide (NaOH) solution of 0.2 M in a round bottom flask of 50 ml, swirled to dissolve completely with a blue coloured solution. 0.504 g (2 mM) of Cimetidine was added into the solution, the colour changed from blue to green with syrupy precipitate. The solution was stirred in a Tekno vetro magnetic stirrer for one (1) hour. Then 0.312 g (2 mM) of 2,2-Bypridine dissolved in 5 ml ethanol was added into the solution, the blue syrupy solution dissolved completely and stirring continued for another one (1) hour. The solution was then filtered into a beaker, and the filterate kept in a cupboard; the residue was kept for (2) two weeks to dry at ambient conditions. The percentage yield was 0.25 g, (20.8%). UV-Vis (ethanol): 241 nm, 279 nm, 450 nm, 755 nm.

2.2.4. Synthesis of [CuCime-phen]SO_4, Complex 4

0.391 g (2 mM) of copper sulfate was dissolved in 4 ml of sodium hydroxide (NaOH) solution of 0.2 M in a round bottom flask of 50 ml, swirled to dissolve completely with a blue coloured solution. 0.504 g (2 mM) of Cimetidine was added into the solution, the colour changed from blue to green with syrupy precipitate. The solution was stirred in a Tekno vetro magnetic stirrer for one (1) hour. Then 0.360 g (2 mM) of 1,10-Phenanthroline dissolved in 6 ml ethanol was added into the solution. The blue syrupy solution dissolved completely and stirring continued for another one (1) hour. The solution was then filtered into a beaker, and the filterate kept in a cupboard. The residue was kept for (2) two weeks to dry in ambient conditions. The percentage yield was 0.35 g, (28%). UV-Vis (ethanol): 260 nm, 291 nm, 446 nm.

3. Results and Discussion

3.1. Physico-Chemical Characterization

The newly synthesized complexes **1-4** are colored, stable at room temperature, partially soluble in common organic solvents such as ethanol, appreciably soluble in dimethylformamide (DMF) and insoluble in water.

The physical properties of the ligands and their metal complexes are given in Table 1 below.

Table 1. Solubility of the ligands and metal complexes in different solvents

S/N	Compounds	Water	Ethanol	Acetone	Acetonitrile	DMF
1	Cimetidine	S/S	S	-	-	S
2	Phenanthroline	S/S	S	S	S	S
3	Bipyridine	S/S	S	S	S	S
4	Imidazole	S	S	S	S	S
5	[Cu-Cime]SO_4 Complex **1**	I	S/S	-	-	S
6	[Cu-Cime-Imi]SO_4 Complex **2**	I	I	SS	-	S
7	[Cu-Cime-Bpy]SO_4 Complex **3**	I	S	-	-	I
8	[Cu-Cime-Phen]SO_4 Complex **4**	I	S	I	I	I

S/S= Slightly Soluble; S= Soluble; I= Insoluble.

The solubility results showed that cimetidine, phenanthroline, bipyridine and imidazole are soluble in ethanol, and slightly soluble in water except for imidazole that is completely soluble in water, acetone, acetonitrile but insoluble in DMF. Complexes **1** to **4** are all insoluble in water. Complex **1** and **2** are soluble in DMF, and are partially soluble in ethanol and acetone respectively. Complex **2** and **5** are insoluble in ethanol, complex **3-4** are insoluble in DMF while complex **3** and **4** are soluble in ethanol.

3.2. Spectra Characterization

3.2.1. Electronic Spectra (UV-Visible spectra)

The electronic absorption spectral data of the ligand and its metal complexes in ethanol and DMF are presented in Table 2. Please note that there is instrument error at about 340 nm and 370 nm in all the UV-Visible spectra.

Table 2. Spectroscopic data of complex 1-4

Complexes	Product yield (%)	Colour	Appearance	Solvent used	Ligands Transitions (nm)	Charge Transfer (nm)	Metal-Ligand charge transfer (d-d transition) (nm)
1	14	Dark Green	Crystalline	DMF	278	313, 370	755
2	84	Dark Blue	Crystalline	DMF	-	370	693
3	20.8	Blue	Powdery	Ethanol	241,297	-	450
4	28	Blue	Powdery	Ethanol	260,291	-	446

The absorption spectra of the complexes and respective ligands were recorded in the range of 200-800 nm. The absorption spectra have been recorded in DMF/Ethanol. The electronic spectra of these ligands and their complexes were illustrated in Table 2. Peaks ranging from 200-300 nm indicates intra-ligand transition (π-π*), peaks at 301-399 nm indicates charge transfer of ligands while peaks at 400-800 nm (Visible region) indicates metal-ligand charge transfer which involves d-d transitions (as a result of the electronic transition of the metal ion). The changes in the absorption spectrum confirm that a new complex has been formed. In particular, the d-d transitions between 400 and 800 nm confirm formation of metal complexes **1-4.**

In complexes **1**, there is a ligand transition at 278 nm and none in complex **2** while charge transfer band appears at 370 nm in both complexes **1** and **2**, in the UV region. At 755 nm and 693 nm respectively, there was metal-ligand charge transfer which indicates a d-d transition (due to Cu^{2+} which is d^9) in the visible region. These changes indicate new products were formed and the appearance of d-d transition confirms complexation between copper and the ligand.

In complex **3** and **4**, there is a ligand transition at 241 nm, 297 nm and 260 nm, 291 nm respectively by both complexes while a no charge transfers for both. At about 450 nm and 446 nm respectively there was metal-ligand charge transfer. This change indicates that a new product has been formed.

Asian Journal of Basic Science & Research
Volume 6, Issue 4, Pages 115-123, October-December 2024

3.2.2. UV-Visible Spectra of Complexes

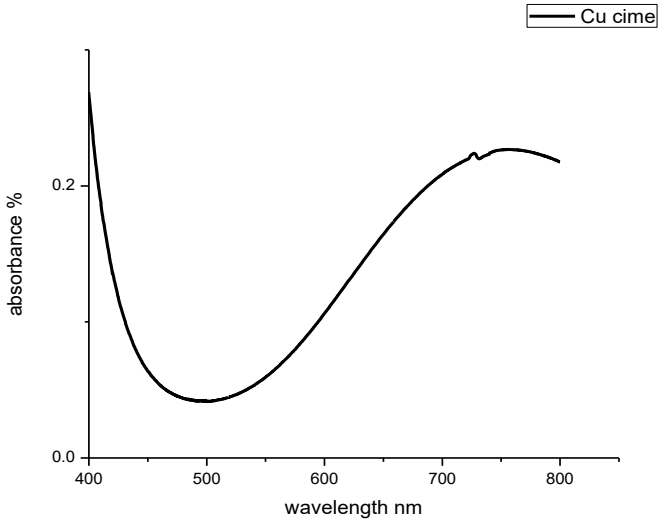

Figure 1. UV-Visible spectrum of complex **1**

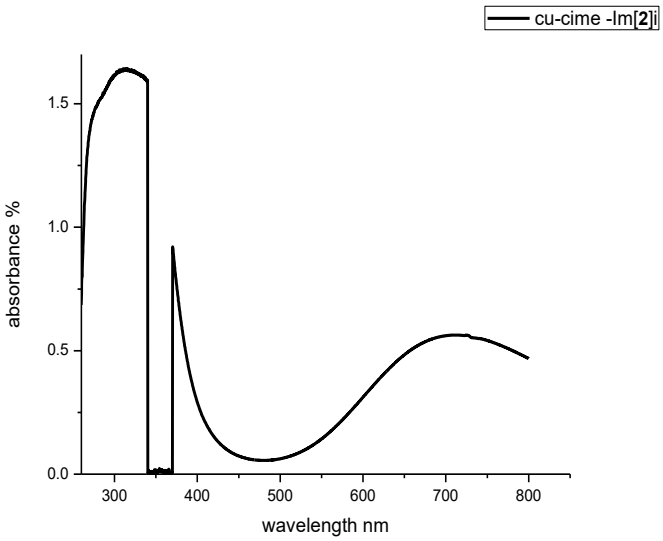

Figure 2. UV-Visible spectrum of complex **2**

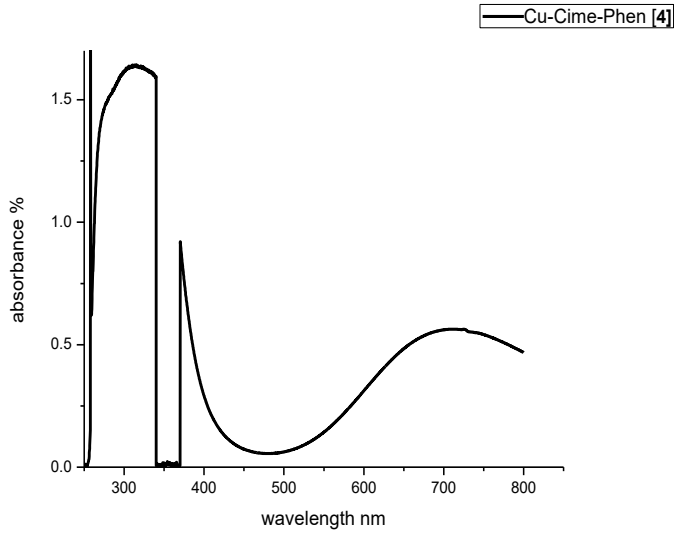

Figure 3. UV-Visible spectrum of complex **4**

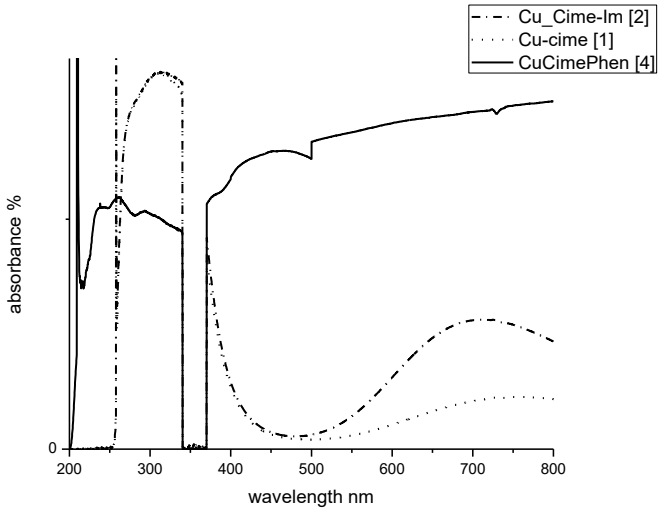

Figure 4. UV-Visible spectrum of complex **1**, **2** and **4**

3.2.3. Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of the synthesized complexes were taken on Shimadzu 8400-S from the region of 400-4000 cm^{-1}. The bonding sites of the complexes through the heteroatoms (O and N) of the ligands were observed in the IR spectrum which is different from the original parent ligands and its metal complexes. The spectra of the parent ligand cimetidine, and its copper complexes are assigned based on literature data (Smith, 1998) and summarized in Table 3 while spectra of two of the complexes (complexes **1** and **4**) were presented in Figures 5 and 6 respectively.

Table 3. FTIR spectra of cimetidine with related complexes

Cimetidine (cm^{-1})	**Cu-Cime (cm^{-1}) complex 1**	**Cu-Cime-Imi (cm^{-1}) complex 2**	**Cu-Cime-Bpy (cm^{-1}) complex 3**	**Cu-Cime-Phen (cm^{-1}) complex 4**	**Assignment**
3144.37	3155.65	3140.22	3107.43	3049.56	N-H stretching
2177.24	2166.13	2166.06	2200.85	2077.40	S-C–N Stretching of Thiocyanates
1590.99	1577.82	1591.33	1566.25	1587.47	N=H, bending of amine
1303.32	1373.36	1371.43	1315.50	1348.29	C-N Stretching of aromatic amine
1157.08	1116.82	1112.96	1157.33	1147.68	C=N Stretching
951.69	983.73	983.73	972.16	983.73	C=C bending
-	-	-	773.48	-	C=N stretching of bpy
-	-	758.05	-	-	C=N stretching of imi
-	-	-	-	719.47	C=N stretching of phen
-	451.00	455.22	418.57	430.14	Cu-N bond formation

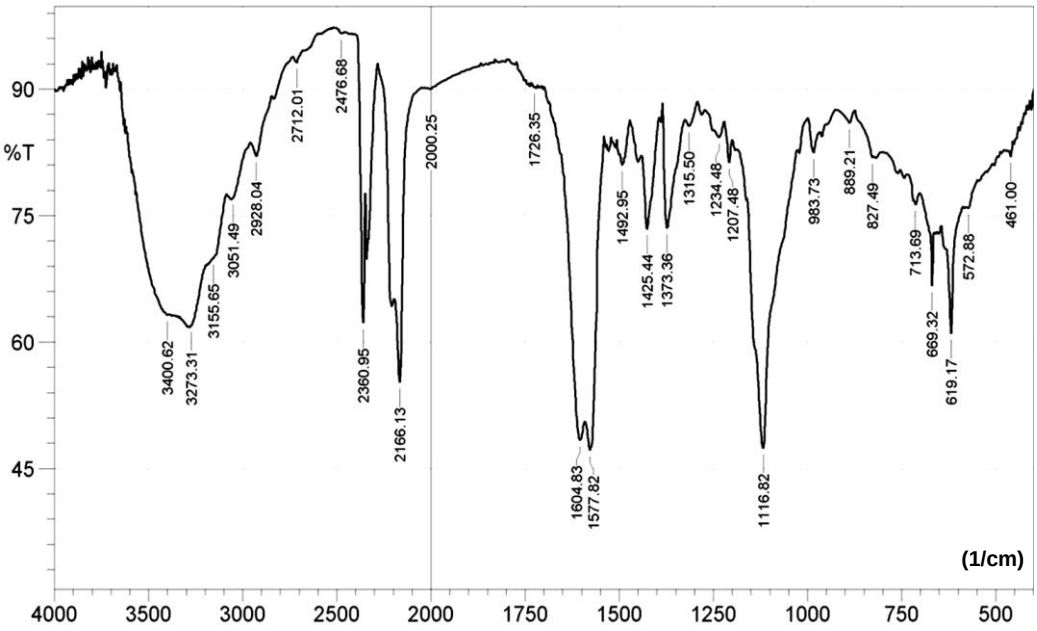

Figure 5. The IR spectrum of CuCime (complex **1**)

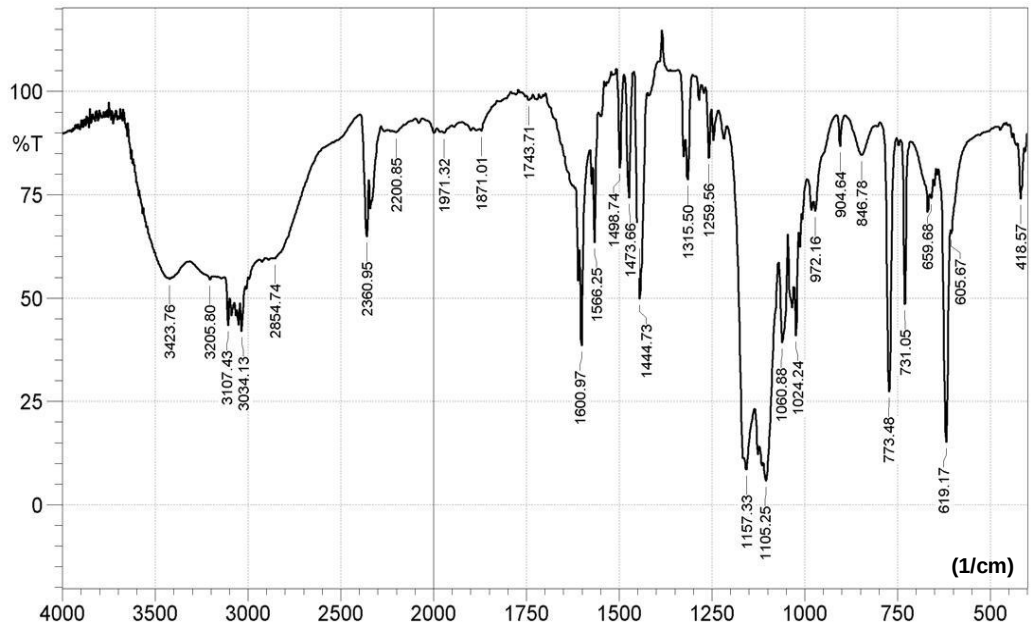

Figure 6. The FTIR of CuCime-Phen (complex **4**)

The FTIR spectral data of cimetidine and its copper complexes reveal significant shifts in key functional group vibrations, confirming coordination between cimetidine and copper. The N-H stretching frequency of the amine group in free cimetidine (3144.37 cm^{-1}) shifts slightly in the complexes (3107.43–3155.65 cm^{-1}), indicating coordination through the nitrogen atom of the amine group. Similarly, the N-H bending frequency shows a shift, further supporting the involvement of the amine in metal coordination.

The S-C≡N stretching frequency of the thiocyanate group also varies (2177.24 cm^{-1} in free cimetidine, shifting to 2166.13–2200.85 cm^{-1} in the complexes), suggesting interaction with the copper center. Significant shifts in the C-N stretching of the aromatic amine group (1303.32 cm^{-1} in free cimetidine, shifting to 1345.29–1373.36 cm^{-1} in the complexes) further confirm the coordination of the aromatic nitrogen to copper.

New bands observed exclusively in the complexes, such as those corresponding to C=N stretching (e.g., 758.05 cm^{-1} for imi, 773.48 cm^{-1} for bpy, and 719.47 cm^{-1} for phen), highlight the contribution of additional ligands to the copper coordination sphere. Low-frequency bands (418.57–455.22 cm^{-1}) represent Cu-N bond formation, providing definitive evidence of metal-ligand bonding.

The FTIR data provides strong evidence for the successful synthesis of the four copper(II) complexes. The presence of Cu-N bands and the characteristic peaks of the co-ligands clearly demonstrate their coordination to the copper ion. The shifts in cimetidine peaks indicate its involvement in complexation. The variations in Cu-N stretching frequencies suggest different coordination environments around the copper center in each complex.

4. Conclusion

This research successfully synthesized four new copper(II) complexes using cimetidine as a primary ligand and incorporating imidazole, 2,2-bipyridine, and 1,10-phenanthroline as secondary ligands. All synthesized complexes and their respective ligands were characterized using UV-Visible spectrophotometry and FTIR spectroscopy. Additionally, solubility tests in various solvents and melting point determinations using a Stuart melting point apparatus were conducted, further confirming the formation of the complexes. The study confirms the chelating ability of imidazole, 2,2-bipyridine, and 1,10-phenanthroline with copper(II) in the presence of cimetidine. For future studies, we recommend the following:

1- Biological Activity Assessment: Investigation of the potential biological activities of the synthesized complexes, including antimicrobial, antifungal, or anticancer properties, to explore their applicability in medicinal chemistry.

2- Thermal Stability Studies: Conduct thermogravimetric and differential thermal analyses to evaluate the thermal stability and decomposition patterns of the complexes as well as further structural characterization studies.

3- Catalytic Applications: Explore the catalytic potential of the synthesized complexes in organic or industrial reactions, such as oxidation or polymerization processes.

Declarations

Source of Funding

This study did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing Interests Statement

The authors declare no competing financial, professional, or personal interests.

Consent for publication

The authors declare that they consented to the publication of this study.

Acknowledgments

The authors thank Department of Chemistry, Federal University Otuoke for facilities and space and International Foundation for Science for the IFS individual research grant awarded to OOA to secure the JASCO-V730 UV-Vis spectrophotometer used to record the UV-Vis spectra of the ligands and complexes.

References

Abosede, O.O., Vyas, N.A., Singh, S., Kumbhar, A.S., Kate, A., Kumbhar, A.A., Khan, A., Erxleben, A., Smith, P., de Kock, C., Hoffmann, F., & Obaleye, J.A. (2016). Copper(II) mixed ligand polypyridyl complexes with doxycycline: Structures and biological evaluation. Dalton Trans., 45: 3003–3012. doi: 10.1039/c5dt04405g.

Chandra, D.R., Ram, N., & Rajesha, S. (2020). Hardness and toughness evaluation of developed Al metal matrix composite using stir casting method. Mater Today Proc., 25: 872–876. https://doi.org/10.1016/j.matpr.2019.12.026.

Direm, A., Abdelbaky, M.S.M., Sayın, K., Cornia, A., Abosede, O., & García-Granda, S. (2018). Sev and pcu topological nets in one-pot newly synthesized mixed-ligand imidazole-containing Cu(II) coordination frameworks: Crystal structure, intermolecular interactions, theoretical calculations, magnetic behavior and biological activity. Inorganica Chimica Acta, Elsevier BV. http://doi.org/10.1016/j.ica.2018.03.011.

Fricker, S.P. (2007). Metal based drugs: from serendipity to design. Dalton Transactions, Cambridge, England, 43: 4903–17. doi: 10.1039/b705551j.

Frota, H.F., Barbosa, P.F., Lorentino, C.M.A., Affonso, L.R.F., Ramos, L.S., Oliveira, S.S.C., Souza, L.O.P., Abosede, O.O., Ogunlaja, A.S., Branquinha, M.H., & Santos, A.L.S. (2024). Unveiling the antifungal mechanisms of CTP, a new copper(II)-theophylline/1,10-phenanthroline complex, on drug-resistant non-albicans Candida species. Biometals: An International Journal on the Role of Metal Ions in Biology, Biochemistry, and Medicine, 37(5): 1237–1253. https://doi.org/10.1007/s10534-024-00605-1.

Obaleye, J.A., & Abosede, O.O. (2019). Fe(III)-doxycycline complexes with diimine ligands: Syntheses, characterization and biological properties. Macedonian Journal of Chemistry and Chemical Engineering, 38(1): 29–38. https://doi.org/10.20450/mjcce.2019.1506.

Ogodo, U.P., & Abosede, O.O. (2019). Synthesis and characterization of Cu (II) complexes of salicylate ligands. Journal of Applied Sciences and Environmental Management.

Smith, B.C. (1998). Infrared Spectral Interpretation: A Systematic Approach (1st Ed.). CRC Press. https://doi.org/10.1201/9780203750841.

Storr, T., Thompson, K.H., & Orvig, C. (2006). Design of targeting ligands in medicinal inorganic chemistry. Chemical Society Reviews, 35(6): 534–544. doi: 10.1039/b514859f.

Trudu, F., Amato, F., Vaňhara, P., Pivetta, T., Peña-Méndez, E.M., & Havel, J. (2015). Coordination compounds in cancer: Past, present and perspectives. J Appl Biomed., 13: 79–103. https://doi.org/10.1016/j.jab.2015.03.003.